IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor/s:	Franklin Okumu
Serial No.:	09/839,684
Filing Date:	April 19, 2001
Title:	SUSTAINED RELEASE FORMULATIONS
Examiner:	Jeffrey E. Russel
Group Art Unit:	1654

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. 1.132

I, Franklin Okumu, hereby state as follows:

1. I am the sole inventor of the subject matter of the above-identified application.

2. I presently work for DURECT Corporation, an assignee of the present application.

3. I previously worked for GENENTECH, Inc., for two years, the other assignee of the present application.

4. My C.V. is attached.

5. I have reviewed the outstanding office action in the above-identified application, as well as two of the cited references:

European Patent Application 0216 485 (EP '485) and U.S. Patent No. 5,747,058 (Tipton et al.).

6. Example 5 of EP '485 is the only example in either EP '485 or Tipton et al. that compares the release rates of compositions that are identical except for the presence of multivalent metal cations (pages 10-14). In this example, compound 1 contains peanut oil, 5% aluminum monosterate and 8 mg/ml of uncomplexed Parlow swine growth hormone; formulation 3 contains peanut oil, 5% aluminum monostearate and 8 mg/ml of zinc complexed growth hormone (page 10, lines 23-31). Tables 4 and 5 (pages 12 and 13) show the serum growth hormone levels for administration of the two compositions over a period of time. The earliest point in time after administration of the growth hormone for which both examples have data is at the 24 hour mark: serum growth hormone was 84.6 ng/ml for the uncomplexed growth hormone, and 40.0 ng/ml for the complexed growth hormone. This shows a decrease in the amount released of about 50% when Zn^{2+} is present.

7. The following experiments were carried out by me, or under my supervision, and are the same experiments described in the above-identified application.

8. Preparation of zinc complexed rhGH: A 20 mg/ml rhGH solution in 25 mM sodium bicarbonate was complexed with zinc at a rhGH:zinc ratio of 10:1. The rhGH/zinc suspension was spray freeze dried to create a fine powder that is approximately 70% rhGH by weight.

9. Preparation of bicarbonate rhGH: A solution of approximately 5 mg/ml rhGH in 10 mM ammonium bicarbonate was lyophilized to produce an excipient free powder.

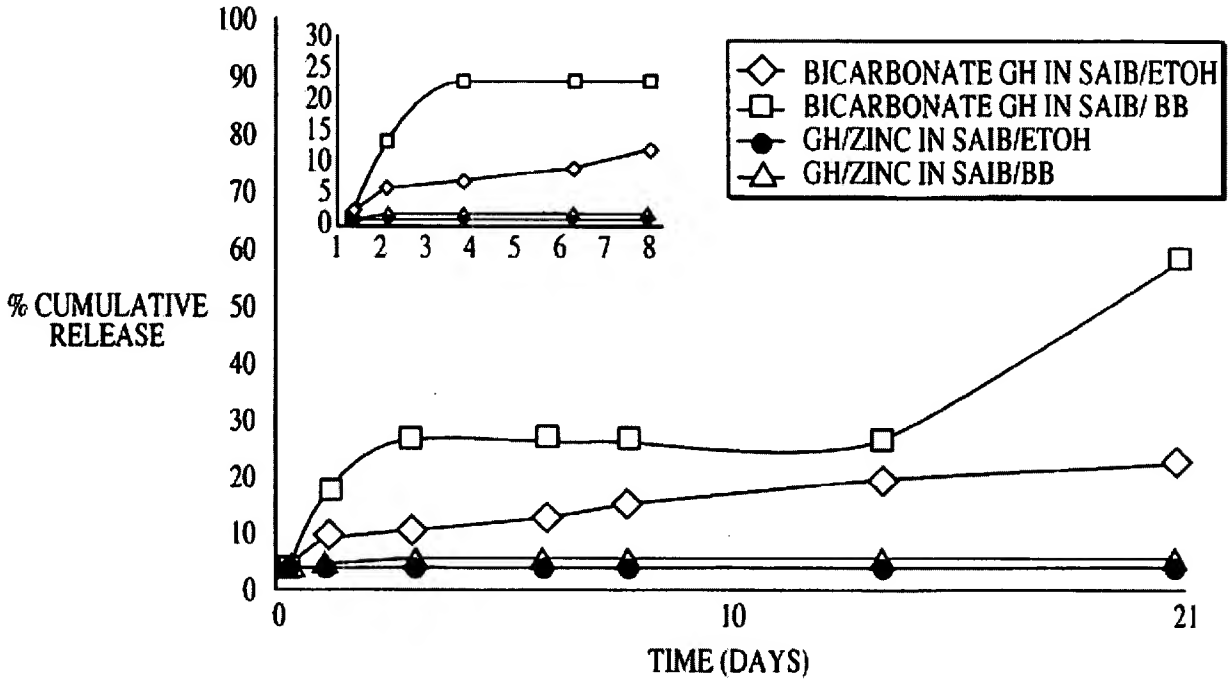
10. SAIB/rhGH suspension preparation: The rhGH SABER suspensions were prepared by mixing rhGH powders with SABER formulations using a shear homogenizer. Release Rate Determination: 0.2 mL of each rhGH/SAIB suspension was added to eppendorf tubes in duplicate, then 0.5 mL of release medium (50 mM HEPES, 10 mM KCl, 0.1% NaN3, pH 7.2) was added above the suspension. The eppendorf tubes were incubated at 37° C and sampled at various time points. At each time point, 0.5 mL of release medium was removed and 0.5 mL of fresh release medium added. Collected samples were stored at -70° C prior to analysis. The release samples were analyzed for protein concentration and protein quality.

11. BCA Assay: The BCA assay in a microtiter plate format was used to determine the protein concentration of the release samples. rhGH protein standards were prepared in release medium at 0, 0.005, 0.01, 0.02, 0.05, 0.2, 0.5 g/ml. 0.02 mL of each blank, standards, and release samples were mixed with 0.2 mL of the BCA working reagent in a microtiter plate. The microtiter plate was incubated at 37° C for 1 hr and the absorbance determined at 562 nm using a microtiter plate reader. The protein concentrations of the release samples were determined from the standard curve using a four parameter non-linear curve fit. The amount of oxidized variants in the rhGH release samples was determined by RP-HPLC. This assay was run using a 4.6x15 cm, 8 mm, 300 angstrom PLRPS column held at room temperature. The mobile phase A contained 50 mM NaH_2PO_4, pH 7.0 and mobile phase B contained 20% propanol in acetonitrile. The separation was isocratic at 49% (B) and the eluent was monitored for absorbance at 214 nm.

12. Size Exclusion Chromatography was used to determine the amount of monomer present in the release samples. This assay was run using a 7.8x300 mm TSK 2000SWXL column held at room temperature. The mobile phase used was 50 mM NaH_2PO_4, 150 mM NaCl pH 7.2 with a flow rate of 1.0 ml/min and a run time of 20 min. 10 g protein was injected and the eluent monitored for absorbance at 214 nm.

13. In vivo pharmacokinetics of rhGH were determined after SC injection of rhGH SABER formulations (SAIB:Benzyl alcohol; 85:15 w/w and SAIB:Benzyl benzoate; 70:30 w/w) in Sprague Dawley (SD) rats. Serum rhGH levels were determined by ELISA (Genentech) with an assay detection limit of 0.1 ng/mL.

14. The effect of zinc on rhGH release from SABER was evaluated by comparing release rates of zinc complexed rhGH and lyophilized rhGH in bicarbonate from SABER. 5% w/v suspensions were prepared using two SAIB/solvent preparations, benzyl benzoate, and ethanol. The release curves are shown in Figure 4. The bicarbonate rhGH produces a higher initial burst than the zinc complexed rhGH for both SABER preparations. The initial burst for the bicarbonate rhGH from SAIB:ethanol is 6.53% compared to 0.53% for the zinc complexed rhGH. The initial burst from SAIB:benzyl benzoate is 14.64% for the bicarbonate rhGH compared to 1.06% for the zinc complexed rhGH. Figure 4 is shown on the following page.



SAIB:SOLVENT	GROWTH HORMONE FORMULATION	% RELEASE OVER 24 HOURS	% DAILY RELEASE 0-21 DAYS
ETHANOL (85:15)	ZINC	0.53	0.10
ETHANOL (85:15)	BICARBONATE	6.53	0.73
BENZYL BENZOATE (70:30)	ZINC	1.06	0.12
BENZYL BENZOATE (70:30)	BICARBONATE	14.64	2.16

FIG. 4

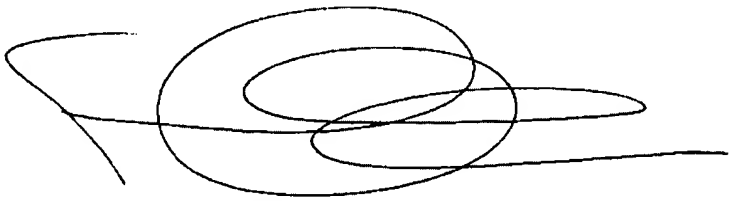
15. The results shown in Figure 4 indicate that the initial burst within 24 hours is reduced more than 10 fold when Zn^{2+} is present, as compared to a composition prepared with ammonium bicarbonate.

16. The results shown in Figure 4 are statistically significant.

17. Figure 9 of the above identified application shows *in vivo* pharmacokinetics of these formulations containing Zn^{2+}, compared to PLGA microspheres. This data demonstrates that the formulations are able to deliver rhGH for prolonged periods of time with a fairly low initial burst.

18. The results shown in Figure 4 are substantially improved and unexpected. Although a small decrease (2 fold) in initial burst might be expected based on the cited references, the actual decrease (10 fold) in initial burst is substantially improved and unexpected.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



30 June 2005
Date

Declarant: Franklin Okumu

CURRICULUM VITAE
Franklin W. Okumu, Ph.D.

PERSONAL DATA

Date of Birth:	February 11, 1969
Citizenship:	U.S.A.
Marital Status:	Married, Wife-Nicole, Son-Niko John (Born December, 20 2003)
Home Address:	3649 Victor Ave. Oakland, CA 94619
Phone:	858-245-5928
E-mail:	fokumu@yahoo.com

EDUCATION

1996:	Ph.D. in Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas.
1994:	Master of Science in Pharmaceutical Chemistry, The University of Kansas, Lawrence, Kansas.
1991:	Bachelor of Science in Chemistry, Antioch College, Yellow Springs, Ohio.

SUMMARY

Pharmaceutical scientist with eight years of industrial experience leading pre-clinical and clinical development programs. An innovative creative thinker with a track record of providing strategic solutions to research and pharmaceutical development problems. Excellent leadership and communication skills have lead to successful completion of corporate and project team goals.

PROFESSONAL EXPERIENCE

Durect Corp. (2004-Present)	Executive Director, Product Development responsible for pharmaceutical product development
Optimer Inc: (2003-2004)	Associate Director, Pharmaceutical Science responsible for pharmaceutical development of carbohydrate vaccines, sustained release anti-inflammatory compounds and antibiotics. Experienced with pre-clinical GLP formulation support, clinical manufacturing, ICH regulatory requirements, cGMP chemistry manufacturing and control requirements for biologics, vaccines and drugs. -Authored novel antibiotic pre-IND package and US IND. -Managed Fast Track product through Phase II clinical trials. -Primary contact for the US FDA. -Responsible for Phase I, II & III clinical program design. -Principal investigator on NIH SBIR Grant. -Implemented electronic data capture solution for clinical data. -Negotiated service contracts with vendors.

Optimer Inc: (2002-2003)	Manager, Formulation and Analytical Chemistry
Genentech Inc: (1999-2001)	Scientist, in the Pharmaceutical Research and Development Department developing methods for analytical characterization, stabilization, manufacturing and delivery of recombinant protein vaccines and therapeutic proteins. Further developing novel technology platforms for sustained local or systemic delivery of therapeutic recombinant proteins and peptides. -Developed clinical formulation for Omnitarg™ antibody. -Authored US IND CMC section for Omnitarg™ antibody. -Developed novel protein sustained release injectable system. -Designed an aseptic half-suit isolator lyophilization facility. -Negotiated service contracts with vendors.
Aradigm Corp: (1996-1999)	Scientist, in the Pharmaceutical Sciences Department developing and manufacturing stable formulations containing recombinant therapeutic proteins and small organic molecules designed for use in a novel pulmonary delivery system AERx™. Experienced with clinical manufacturing, ICH stability requirements, cGMP chemistry manufacturing and control requirements for biologics. Management experience was also gained by supervising 3 direct reports. -Responsible for clinical manufacturing for five human trials. -Authored CMC section for insulin pre-IND and US IND. -Lead CMC subteam for inhaled insulin project. -Lead multi-functional project teams.
The University of Kansas: (1991-1996)	Worked with Dr. Ronald T. Borchardt on the delivery of peptides, specifically on determining which structural features influence the permeability of peptides. Experienced with methods used for peptide synthesis (e.g., solid phase synthesis), purification of peptides (e.g., preparative HPLC, lyophilization), structural characterization (CD, NMR, MS, SEC) and analysis of peptides (e.g., HPLC, CZE). Experience was also obtained using 1D and 2D NMR and molecular modeling so as to determine peptide solution structures. Teaching assistant in the pharmaceutics laboratory course for pharmacy students.
Genentech Inc: (Sept, 1995-January, 1996)	Worked with Dr. Jeffrey L. Cleland on the microencapsulation of peptides, specifically on determining how structural features influence the rate of peptide release. Experience with encapsulation techniques and methods used

for *in vitro* evaluation of microspheres (e.g. SEM, SEC). This was an industrial internship, which was part of my Ph.D. program at The University of Kansas.

Antioch College: (1986-1991)
Worked with Dr. Stanley Bernstein on the synthesis of 3-amino-2-chloro-5,6-dimethoxyquinoline, a precursor to an isothiocyanate based fluorescent tagging reagent for primary and secondary amines.
Teaching assistant in the general chemistry laboratory course (Winter quarter, 1991).
Teaching assistant in the general physics laboratory course (Spring quarter, 1990).
Teaching assistant in the general chemistry laboratory course (Fall quarter, 1989).

The University of Kansas: (Summer, 1990)
Worked with Dr. Richard S. Givens on the synthesis of transition-state analogs of the 2,3-napthalenedicarboxaldehyde(NDA) derivitization reaction. These analogs were used to grow antibodies, which were then screened for catalytic activity.

Yellow Springs Instrument: Co. (Spring, 1989)
Set up an on-line information services center for the research and development department.

The University of Cincinnati: (Summer, 1988)
Worked with Dr. Richard Scott on a lead abatement pilot study. This study was done to develop a protocol that could be used to determine how much elemental lead was present in abated and non-abated areas.

CAREER GOALS

To make significant contributions toward treating or eradicating diseases that afflict global populations.

FELLOWSHIPS & AWARDS

NIH-Small Buisnes Inovation Research (SBIR)
Principal Investigator (2003-04)
NIGMS-University of Kansas Biotechnology Predoctoral Fellow (1992-95)
The University of Kansas Black Faculty and Staff Scholar (1994-95, 1995-96)
Dayton Science and Engineering Foundation Grant (1990-91)

PROFESSIONAL AFFILIATIONS

ACS, member
AAPS, member
CRS, member
AAPS Student Chapter, University of Kansas, President (1995-96)

MANUSCRIPTS

Okumu, F.W., Cleland, J.L., Implants and Injectables in Modified-Release Drug Delivery Technology, Drugs and the Pharmaceutical Science Series. Edited by Rathbone, M., Hadgraft, J., Roberts, M., Marcel Dekker, Inc New York 2003

Cai, L., Okumu, F.W., Cleland, J.L., Beresini, M., Hogue, D., Lin, Z., Filvaroff, E. A slow release formulation of insulin as a treatment for osteoarthritis. Osteoarthritis Cartilage. (2002) 10(9) pp. 692

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Okumu, F.W., Yun-Lee, R., Blanchard, J., Cipolla, D., Woods, C., Llyod, P., Okikawa, J., Gonda, I., Farr, S., Rubsamen, R., Adjei, L., Bertz, R. Evaluation of the AERx™ pulmonary delivery system for systemic delivery of a selective D1 agonist, ABT-431. *Pharm. Res.* 19 (2002) pp. 1010-13

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Pauletti, G.M., Gangwar, S., Okumu, F.W., Siahaan, T.J., Stella, V.J. and Borchardt, R.T. Enzyme-sensitive cyclic prodrugs of peptides: in vitro evaluation of the acyloxyalkoxycarbamate pro-moiety in a model hexapeptide. *Pharm. Res.* 13 (1996) pp. 1615-1623

Pauletti, G.M., Gangwar, S., Knipp, G.T., Nerurkar, M.M., Okumu, F.W., Tamura, K., Siahaan, T.J. and Borchardt, R.T. Structural requirements for the intestinal absorption of peptide drugs. *J. Controlled Release*. 41 (1996) pp. 3-7

ABSTRACTS

Okumu, F.W., Daugherty, A., Dao, L.N., Fielder, P.J., Brooks, D., Sane, S. and Cleland, J.L. Sustained delivery of growth hormone from a novel injectable liquid, PLAD. International Symposium for Controlled release of Bioactive Materials, 28th Session, June 25-28, 2001.

Okumu, F.W., Daugherty, A.D., Dao, L.N., Fielder, P.J., Brooks, D., Sane, S., Sullivan, S.A., Tipton A.J. and Cleland, J.L. Evaluation of the SABER™ delivery system for sustained release of growth hormone—Formulation design and *in vivo* assessment. International Symposium for Controlled release of Bioactive Materials, 28th Session, June 25-28, 2001.

Duenas, E.T., Okumu, F.W., Daugherty, A.D. and Cleland, J.L. Sustained delivery of rhVEGF from a novel injectable liquid, PLAD. International Symposium for Controlled release of Bioactive Materials, 28th Session, June 25-28, 2001.

Okumu, F.W., Sullivan, S.A., Tipton A.J. and Cleland, J.L. Evaluation of SABER™ as a Local delivery system for rhVEGF—Formulation design and in vitro assessment. International Symposium for Controlled release of Bioactive Materials, 27th Session, July 10-13, 2000.

McElduff, A., Farr, S., Ward, E., Okumu, F., Mather, L., Gonda, I., Rubsamen, R., Dimarchi, R., Wolff, R. Comparison of the pharmacokinetics and pharmacodynamics of subcutaneous and inhaled insulin lispro in healthy fasted volunteers. American Diabetes Association 58th Scientific Sessions, June 13-16, 1998.

Farr, S., McElduff, A., Ward, E., Okumu, F., Mather, L., Gonda, I., Rubsamen, R. A comparison of the pharmacokinetics and pharmacodynamics of inhaled insulin administered as different strength solutions to healthy volunteers. American Diabetes Association 58th Scientific Sessions, June 13-16, 1998.

Okumu, F.W., Cleland, J.L. and Borchardt, R.T. The effect of size, charge and conformation on the release kinetics of peptides from biodegradable microspheres. *Pharm. Res.* **13** (Suppl.) Abstract #BIOTEC 2030

Okumu, F.W., Pauletti, G.M., Vander Velde, D.G., Siahaan, T.J. and Borchardt, R.T., The effect of conformational flexibility on the permeability of a hexapeptide across monolayers of a cultured human intestinal epithelial cell (Caco-2 cells). *Pharm. Res.* **12** (Suppl.) S-302 Abstract #PDD 7437

Okumu, F.W., Pauletti, G.M., Vander Velde, D.G., Siahaan, T.J. and Borchardt, R.T. The effect of charge and conformation on the permeability of a hexapeptide across monolayers of a cultured human intestinal epithelial cell (Caco-2 cells). *Pharm. Res.* **12** (Suppl.) S-302 Abstract #PDD 7438

PRESENTATIONS

Okumu, F.W., Darling, S, Dao, L.N., Fielder, P.J., Sullivan, S.A., Cleland, J.C. SABER Provides Burst Free Release of Growth Hormone From PLGA Microspheres. Millennial World Congress of Pharmaceutical Sciences Meeting, San Francisco, California. April 16-20, 2000

Okumu, F.W., Yun-Lee, R., Blanchard, J., Cipolla, D., Woods, C., Llyod, P., Okikawa, J., Gonda, I., Farr, S., Rubsamen, R., Adjei, L., Bertz, R. Evaluation of the AERx™ pulmonary delivery system for systemic delivery of a selective D1 agonist. American Association of Pharmaceutical Scientists Annual Meeting, San Francisco, California. November 15-19, 1998

Okumu, F.W., Pauletti, G.M., Vander Velde, D.G., Siahaan, T.J. and Borchardt, R.T. The effect of conformation flexibility on the permeability of a hexapeptide across monolayers of a cultured human intestinal epithelial cell (Caco-2 cells). 28th Annual Pharmaceutics Graduate Student Research Meeting, Minneapolis, Minnesota. June 28-30, 1996

Okumu, F.W. The effect of structural modification on the transport of a hexapeptide across monolayers of Caco-2 cells. Department of Pharmaceutical Research and Development Genentech, South San Francisco, California. January 9, 1995

Okumu, F.W. The effect of structural modification on the transport of a hexapeptide across monolayers of Caco-2 cells. Department of Pharmacy University of California San Francisco, San Francisco, California. December 12, 1995

Okumu, F.W., Pauletti, G.M., Vander Velde, D.G., Siahaan, T.J. and Borchardt, R.T. The effect of conformation flexibility on the permeability of a hexapeptide across monolayers of a cultured human intestinal epithelial cell (Caco-2 cells). 27th Annual Pharmaceutics Graduate Student Research Meeting, Ann Arbor, Michigan. June 22-24, 1995

Carlson, R.G., Givens, R.S., Okumu, F.W., Schowen, R.L. and Wilson, G.S. Synthesis of transition-state analogs of the 2,3-naphthalenedicarboxaldehyde (NDA) derivatization reaction: applications of catalytic antibodies to analytical chemistry. 25th Midwest Regional American Chemical Society Meeting, Manhattan, Kansas. November 7-9,1990.

Carlson, R.G., Givens, R.S., Okumu, F.W., Schowen, R.L. and Wilson, G.S. Synthesis of transition-state analogs of the 2,3-naphthalenedicarboxaldehyde (NDA) derivatization reaction: applications of catalytic antibodies to analytical chemistry. First Annual Argonne Symposium for Undergraduates in Science, Engineering and Mathematics, Chicago, Illinois. November 2 and 3, 1990.

ISSUED PATENTS AND PATENT APPLICATIONS

Title: USE OF INSULIN FOR THE TREATMENT OF CARTILAGENOUS DISORDERS
US Patent No. US6689747

Title: SUSTAINED RELEASE FORMULATION
US Patent Application No. 20030045454

Title: ERODIBLE POLYMERS FOR INJECTION
US Patent Application No. 20020173552

Title: SUSTAINED RELEASE FORMULATIONS
US Patent Application No. 20020001631

Title: TIACUMICIN PRODUCTION
PCT Serial No. PCT/US03/21977

Title: NEW METHOD OF USE OF KNOWN COMPOUNDS
US Provisional Application No. 60/507,716

Title: TREATMENT OF A CONDITION IN A MAMMAL WITH ADMINISTRATION OF COMPOUNDS AND METHODS OF USE THEREOF
US Provisional Application No. 60/524,698

Title: TREATMENT OF A DEGENERATIVE CARTILAGE CONDITION IN A MAMMAL WITH GLYCOSIDASE INHIBITORS
US Provisional Application No. 60/531,168

REFERENCES

Available on Request